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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,495	01/02/2002	Wen Liang Yan	0249-0002US	7029

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EXAMINER	
QIAN, JANICE LI	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,495	YAN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-33* is/are pending in the application.

4a) Of the above claim(s) *28 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group V **without** traverse and species election for producing a HS cell depository of immunotyped homozygous stem cells is acknowledged. Claims 28 and 30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 29 and 31-33 are under current examination.

Drawings

New corrected drawings are required in this application because figures 8 and 10 are considerably out of the center of the pages. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 31, 32 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a credible asserted or a well-established utility.

Claims are drawn to a method for producing an immunotyped human homozygous stem cell depository useful for transplantation in humans. The specification teaches that the immunotyped HS cells have reduced immunogenicity, and would reduce the demand on tissue typing resources. However, neither the specification as filed nor any art of record suggest that human homozygous pluripotent stem cells are obtainable by the claimed method so that a practical utility could be well established (see detailed discussion following). Numerous pre- and post-filing publications indicate that considerable research is needed before human pluripotent stem cells could become a practical therapeutic regimen. Therefore, the claimed method is not supported by a credible or well-established utility.

Even if the human HS cells are obtainable, the only utility for establishing a cell depository is to carry out further research characterizing the homozygous stem cells, which is not considered as specific and substantial. Thus, the cell depository, thus, the method of establishing such has no specifically identified utility, rather, the specific utility of the HS cells requires further research to identify or reasonably confirm. (see Brenner, Comr. Pats. v. Manson, 148 USPQ 689 (US SupCt 1966).

Applicant is referred to the Revised Utility Examination Guidelines published December 21, 1999 in the Federal Register, Volume 64, Number 244, pages 71441-

71442 for the required *specific* and *substantial* utility. "A CLAIMED INVENTION MUST HAVE A SPECIFIC AND SUBSTANTIAL UTILITY. THIS REQUIREMENT EXCLUDES 'THROW-AWAY' 'UNSUBSTANTIAL', OR 'NONSPECIFIC' UTILITIES," (column 3, 3rd paragraph of page 71441). In the current office practice, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not *substantial* utilities. Similarly, a general statement of a utility for further cell biology study would ordinarily be insufficient.

Accordingly, the claimed invention is not supported by a substantial asserted utility, creditable asserted utility, or a well-established utility for the reasons set forth above.

Claims 29, 31, 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Specifically, since the claimed invention is not supported by either a credible asserted or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Claims 29 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claims are drawn to a method for producing an immunotyped homozygous stem cell depository. The specification teaches that the immunotyped HS cells have reduced immunogenicity, and could be useful for stem cell transplantation to reduce or prevent immune rejection. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. Thus, the claimed method clearly or implicitly encompasses establishing a stem cell bank for clinical transplantation including and particularly for human stem cell therapy, therefore, the claims will be evaluated by that standard as whether the claimed HS cells are enabled for such use.

The claims are drawn to a method of establishing a homozygous cell bank, wherein the stem cells are derived from non-fertilized germ cells using the art known parthenogenetic oocyte activation. The specification teaches that mitotically activated non-fertilized mouse oocyte forms a blastocyst-like mass, and after 15 days of co-culture on murine embryonic feeder cell layer and ES medium, the inner cell mass could be obtained for further isolation of pluripotent stem cells (example 1a). From example 1(b) to example 1(e), it appears that the same was done with human oocyte, and various methods (kidney capsule implant, differentiation within teratomas) were used to verify that the cells obtained from the mass are indeed pluripotent, i.e. capable of developing into three layers, ectodermic, mesoderm, and endoderm. However, in a post-filing publication by the applicants (Stem Cells 2003;21:152-61), only *mouse* pluripotent stem cells were obtained. Applicants admitted "SO FAR, FURTHER CULTURING OF THE [human] INNER CELL MASSES PRODUCED BY THIS ACTIVATION METHOD HAS NOT BEEN SUCCESSFUL" (mid-section, right column, page 158). In view of such, the claimed invention does not appear to be enabled for making *human* homozygous stem cells in the absence of clarification of the contradictory evidence found in the reference.

Clarification is important in view of the state of the prior art with regard to stem cells generated by parthenogenetic oocyte activation. For example, *Newman-Smith et al* (Development 1995;121:2069-77) teach that stem cells obtained from parthenogenetic peri-implantation embryos are defective, i.e. ICMs from parthenotes failed to maintain undifferentiated stem cells, and differentiated almost exclusively into parietal endoderm (e.g. abstract). *Park et al* (Jpn J Vet Res 1998;46:19-28) teach parthenogenetic

embryonic stem cells retarded in growth and showed restricted differentiation compared to their fertilized counterpart (e.g. abstract). Moreover, it is well known in the art that human ES cells are distinct from mouse ES cells in many aspects. For example, *Draper et al* (Curr Opin Obstet Gynecol 2002;14:309-315) teach, "RESEARCH USING MOUSE EMBRYONIC STEM CELLS HAS YIELEDED PROTOCOLS FOR INDUCING THE DIFFERETIATION OF EMBRYONIC STEM CELLS INTO A VARIETY OF CELL LINEAGES. HOWEVER, HPSCS AND MURINE PLURIPOTENT STEM CELLS DIFFER IN VARIOUS RESPECTS, AND IT REMAINS TO BE SEEN WHETHER THESE PROTOCOLS ARE DIRECTLY TRANSFERABLE TO HPSCS" (right column, page 309).

The HS cells appear to be obtainable from mouse parthenogenetic blastocyst-like inner cell mass, and assuming human HS cells could be obtained by the claimed methods, however, using such for clinical transplantation does not appear to be enabled in light of the teachings of the skilled artisan. In a post-filing publication, *Draper et al* (Curr Opin Obstet Gynecol 2002;14:309-315) teach, "CURRENT RESULTS DO INDICATE THAT DIFFERETIATION OF HUMAN PLURIPOTENT STEM CELLS INTO A RANGE OF CLINICALLY USEFUL CELL TYPES IS POSSIBLE. HOWEVER, CONSIDERABLE RESEARCH IS NECESSARY BEFORE TREATMENTS USING TRANSPLANTATION OF HPSC-DERIVED TISSUES MAY BECOME A PRACTICAL REALITY" (right column, page 309, emphasis added). *Donovan and Gearhart* (Nat 2001 Nov;414:92-97) teach "IF STEM CELLS ARE TO BE USED TO TREAT A WIDE VARIETY OF HUMAN DISEASES, THEN WE WILL NEED TO OVERCOME SEVERAL FORMIDABLE CHALLENGES. STEM CELLS WILL BE NEEDED IN LARGE QUANTITIES AND BE ABLE TO DIFFERENTIATED IN A CONTROLLED MANNER TO FORM HOMOGENEOUS POPULATIONS OF CELLS THAT ARE HISTOCOMPATIBLE WITH AN INDIVIDUAL" (left column on page 95). *Odorico et al* (Stem Cells 2001;19:193-204) detailed the major barriers for using EM stem cell lines for routine therapeutic purpose in addition to the

danger of immune rejection. They teach that the efforts have been hampered a). by the inability to selectively differentiating human ES cells to a particular cell type of interest and to purify this lineage from the mixed population; b). by the inability to demonstrate that the differentiated cells and cellular derivatives function in a normal physiologic way, because differentiated ES cell cultures can contain multipotent progenitors as well as terminally differentiated cells. Many fetal or embryonic tissues and multipotent cells are functionally immature, one cannot assume that all ES cell progeny will subserve normal cellular physiologic functions; c). by the requirement of integration of the transplanted cells into the existing host tissue in a functionally useful form; d). by the possibility that human ES cell derivatives may form tumors in human recipients (see particularly, pages 198-200). The specification fails to teach how to overcome the aforementioned difficulties in the art. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Claims encompass using any type of germ cells, i.e. both oocyte and sperm cells. However, neither the prior art of record nor the specification teaches how to mitotically activating a sperm cell, and whether such germ cell could develop a blastocyst-like mass, and whether pluripotent stem cells could be obtained. Given the unpredictability in the art, it would have required undue experimentation to practice the invention as it is broadly claimed. According to the teaching of the specification and the post-filing publication (*Lin et al*), it appears only female HS cells could be obtained.

Claims encompass using various methods for HS cell immunotyping. The specification teaches serological and molecular techniques, for example. However, the

specification fails to teach whether serological techniques are suitable for HS cell typing since these cells are pluripotent, and yet to develop mature HLA serotypes.

Accordingly, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation, "post-meiosis I diploid germ cells". Given the plain meaning, "post-meiosis I" germ cells appear to be germ cells in the meiotic division phase II, which are haploid rather than diploid (see fig.20-16, *Alberts et al,* Molecular Biol Cell 1994). Example I of the specification teaches a method wherein germ cells of meiotic phase II (non-fertilized oocyte) was mitotically activated. In view of such, it is unclear what stage germ cells are encompassed by the claims, thus the metes and bounds of the claims are uncertain.

Claim 29 is vague and indefinite because of the term "homozygous stem cells". From the claims, it is unclear what characteristics the term "homozygous" defines, the size, type, or MHC homozygosity and genomic loci of the stem cells, thus, the metes and bounds of the claims are unclear.

Claim 29 is vague and indefinite because of the claim recitation, "stem cells". Since there are many types of stem cells, such as totipotent, pluripotent, and tissue-specific stem (progenitor) cells, it is unclear which type of stem cells the claim encompasses. It is noted that the specification teaches that the claimed HS cells are pluripotent (Specification, page 6, last paragraph), yet the claims encompass EM stem cells or tissue specific progenitor cells.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942 (571-272-0730, after the Office relocation in January, 2004). The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
December 22, 2003